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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,452	10/19/2005	Fabio Giannessi	4865-8	6827

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,452	GIANNESSI ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-17* is/are pending in the application.

4a) Of the above claim(s) *3-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 4/14/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the rejection under 25 USC 2nd paragraph have been fully considered but they are not persuasive:

Claims 10-13 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is added to this rejection, necessitated by the newly added claim.

Applicant argues the terms “subpharmacological”, “subpharmaceutical” and “pharmacological” have meanings as understood by one having ordinary skill in this art; a “pharmaceutical” dose for ST1326 is 100 mg/kg/day and for metformin is 900 mg/kg/day; “subpharmacological" are doses lower than "pharmaceutical", such as 30 mg/kg for ST1326 and 200 mg/kg for metformin. While this argument does give example doses that fall within the terms, the issue of where the line falls between the terms is still not clear. As pointed out on the record, Dagogo-Jack teaches dosing with metformin does not result in an optimum glycaemic effect (a “pharmacological” dose) at the same dose for each patient; a dose titration, starting at 500 or 850 mg (7.1 or 12.1

mg/kg for a 70 kg individual), is required to determine effective amounts, the "pharmacological" dose. The point is that a given amount of each drug in a formulation would fall within the metes and bounds of the claims for one patient, but the exact same doses would be outside of the claim boundaries when administered to a different patient. Therefore, the rejection is still maintained.

3. Applicant's arguments, see pp. 6-7, filed 4/14/2008, with respect to the rejection of claims have been fully considered and are persuasive in part. The rejection of claim 10 has been withdrawn. The rejection of claims is maintained:

Claims 1, 9 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giannessi, et al. (1999; WO 99/59957 A1; IDS reference; referred to as Giannessi (1999)) in view of Giannessi, et al. (2003; "Discovery of a Long-Chain Carbamoyl Aminocarnitine Derivative, a Reversible Carnitine Palmitolytransferase inhibitor with Antiketotic and Antidiabetic Activity"; J. Med. Chem.; 46: 303-309; published online 12/17/2002; IDS reference; referred to as Giannessi (2003)) and Dagogo-Jack ("Pathophysiology of Type 2 Diabetes and Modes of Action of Terapeutic Interventions"; Arch. Intern. Med.; 1997; 157:1802-1817; IDS reference).

Applicant argues that the synergistic effect for the combination of ST1326 at 30 mg/kg and metformin at 200 mg/kg (both drug concentrations within the "subpharmacological" range), overcomes the obviousness rejection. This argument is persuasive for claims that are limited to concentrations of both compounds in the subpharmacological range (claims 10 and 17), but no such evidence is of record for any

other concentrations of the two compounds; none of the claims maintained in the rejection are limited to concentrations where synergistic data have been reported.

Applicant argues the person of ordinary skill in the art would not find any suggestion in the Gianessi (1999) reference to choose ST1326 from the large number of compounds of formula (I) and to specifically combine it with metformin, one of many possible biguanides. This argument is not persuasive; as present in the record it would have been obvious to select ST1326 because of the lowest IC_{50} value reported in Table 1, it is noted that the IC50 is the 2nd lowest value of all values reported for all methods used to measure the value. This factor gives significant motivation to select ST1326. The combination with a biguanide is recited in the same paragraph where it is stated the combination is with a "well-known" active ingredient. The Diaggo-Jack demonstrated metformin is one of one approved antidiabetic biguanides (Table 3); i.e., the teaching of a "well-known" drug that is also a biguanide indicates metformin to one of ordinary skill in the art. Additionally, it would have been obvious to select the combination based on the fact that both compounds have an art-recognized equivalent activity for treating type 2 diabetes and insulin resistance.

Applicant argues facts with respect to the synergistic effects, which hasve been addressed above. The argument is also presented that one of skill in the art would not be encouraged to combine ST1326 with metformin at concentrations lower than the doses disclosed and argued as "pharmacological"; 100 mg/kg/day ST1326 and 900 mg/kg/day for metformin. This argument is not persuasive, except for the case of claim 10 and 17, where applicants synergistic data is demonstrated. With respect to other

conditions, it would have been obvious to use lower doses of one or both drugs, for the reasons of record.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 9-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is necessitated by the claim amendment. The amended phrase "forming metformin" in the 2nd and 3rd lines of claim 1 is new matter, not present in the disclosure as filed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 and 9-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is necessitated by the claim amendment. It is not clear what is meant by the phrase "forming metformin" in the 2nd and 3rd lines of claim 1. "Forming" implies a method step, within a composition of matter claim, rendering the scope of the

claims unclear. A review of the specification did not identify any explanation of the formation process implied.

Conclusion

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614